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Session M19: Bimodality vs. Trimodality in Stage III NSCLC

M19-01 Bimodality vs. Trimodality in Stage III NSCLC, Thur, Sept 6, 10:30 - 12:00

Treatment of IIIA overview

Putnam, Joe B.

Vanderbilt University Medical Center, Nashville, TN, USA

The management of IIIA NSCLC challenges the surgeon and the multidisciplinary team given the heterogeneity of the local disease and the variable incidence of regional and systemic metastasis. Invasive staging with pathology examination of lymph node or other tissues further describes the clinical extent of the disease to refine treatment decisions. Patients with involved N2 nodes should be preferentially considered for entry into a prospective clinical trial, or therapy with local and systemic treatment(s).

Induction therapy has been undertaken to improve survival in patients with clinical stage IIIA (N2) disease. Recent multi-institutional studies [1] have suggested a benefit from induction chemotherapy. Adjuvant therapy has shown survival benefit in various prospective randomized clinical trials and meta-analyses. [2, 3]

The North American Intergroup 0139 phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs. CT/RT followed by surgical resection (S) for stage IIIA (pN2) NSCLC was designed to evaluate the role of resection after chemotherapy and radiation therapy. Pneumonectomy accounted for 14/15 postoperative deaths and may have compromised overall survival. The study showed that 1) progression free survival was better with resection after chemoradiotherapy, 2) a non-significant survival advantage was shown with CT/RT+S; 3) pN0 status was associated with prolonged survival, and 4) although S may be considered in fit patients, the results with pneumonectomy are no different than with CT/RT alone.[4]

The down-staging identified with induction therapy is important in identifying patients with improved chances for survival. Patient with persistent N2 disease after induction therapy have poorer survival and should not typically be considered as operative candidates. SWOG 8805 (phase II) evaluated induction chemoradiotherapy followed by resection for patients with cStage IIIA and cStage IIIB. This strategy provided a pathological complete response in 22%; overall survival (3-years) was 27%. Patients with no residual mediastinal lymph node metastasis had a median survival of 30 months compared to 10 months with residual disease (p=0.0005). [5] Another study identified a complete response rate of 28% following induction chemoradiotherapy. 5 year survival was 35.8% compared to 9% with residual nodal disease (p=0.023).[6] Alternatives to the initial mediastinal staging include esophageal ultrasound (EUS) and transbronchial ultrasound (TBUS) Resection should be avoided after induction therapy in patients who have biopsy-proven residual tumor in the mediastinal nodes. The benefit of resection over and above that achieved with combined chemotherapy and radiation therapy is small and may carry significant operative and perioperative risk. If only a lobectomy would be performed, 5 year survival may reach 40% following induction CT/RT.

Selection of optimal treatment for patient with NSCLC requires excellent pretreatment staging and clinical evaluation with discussion of all therapeutic possibilities by the integrated multidisciplinary care team: thoracic surgeon, pulmonologist, radiation oncologist, medical oncologist, and allied specialties. The clinician balances the risks from local and systemic therapies of NSCLC (local disease control, pain relief, improved survival) and the benefits of improvement in survival and quality of life, based upon the individual patientís characteristics, co-morbidities, clinical stage and perioperative evaluation. Multidisciplinary evaluation, consistency of clinical evaluation and therapeutic approach, application of proven intraoperative and perioperative techniques, completeness of resection, and adequacy of mediastinal lymph node dissection, etc., all benefit the patient by optimizing local control and subsequent therapeutic decisions.

Table 1. Primary Therapy Considerations for IIIA Non-Small Cell Lung Carcinoma

Note: All patients should be considered for participation into therapeutic clinical trials.

- Accurate clinical staging with FDG-PET is essential for optimizing therapeutic recommendations.[7]
- If clinical staging confirms (histologically) metastasis to N2 lymph nodes, chemoradiotherapy is effective.[8]. Following R0 resection, patients with metastasis to N2 lymph nodes should be considered for adjuvant chemotherapy to enhance survival.[2, 3, 9]
- The role of preoperative chemotherapy and radiation therapy for limited stage IIIa is unclear.[4]

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M19-02 Bimodality vs. Trimodality in Stage III NSCLC, Thur, Sept 6, 10:30 - 12:00

Bi-modality versus tri-modality therapy in stage IIIa NSCLC: Where does the data lead us?

Turrisi, Andrew T.

Department of Radiation Oncology, Wayne State University, Detroit, MI, USA

Improving survival outcomes for patients presenting with mediastinal lymph nodes, Stage IIIa, N-2, motivates thoracic surgeons, medical oncologists and radiation oncologists alike. All desire the best treatment for the most patients, but we continue to debate what current tactics are most likely to result model that we can readily adopt. With an eye to the future, most hope that a gene array or molecular identifier will forecast which patients have tumors with genetic packages that are amenable to curative therapy. Alas, we are not to that point today, and the 30% of NSCLC patients with heterogeneous stage IIIa disease variously are treated with the best of intentions based on a rather weak foundation of clinical trials. All stage IIIa is not the same, and a one-size fits all, bi- or tri- modal therapy is likely to be error-prone and unsatisfactory to us all. What is abundantly clear is that no single modality alone is appropriate, and the wish for surgery to be the most successful tactic leads us into the temptation to use it more widely than appropriate for the extant data. The same can be said for radiotherapy alone, which is clearly inferior to radiotherapy plus chemotherapy in patients that can tolerate chemotherapy. Unlike the stringent winnowing process selecting patients for surgery, radiotherapy discriminates less and can more easily be applied to the entire population presenting with lung cancer. Poor heart and lung functions are not the same barrier for radiotherapy as these are for surgery. The presence of N-2 nodes indicates that the deranged tumor cell-line has metastatic potential beyond the thorax, more likely than not. Thus, it is quite clear that the use of chemotherapy in N-2 patients is desirable on theoretic grounds (they metastasize) and clinical data (survival) is better, but we must remember that the studies done supporting that always mandate that the patients have good performance status and can withstand systemic therapy. Cisplatin is the most universally accepted drug, but pairing it with another agent has not resulted in a combination that everyone is willing to use. Europeans have recognized this and allowed investigator physicians to choose what other drug to add to cisplatin.

The landmark CALGB study initiated in 1984 established that this platinum-based chemotherapy added to radiotherapy was better than radiotherapy alone (Dillman). Over the ensuing two decades, there have been nationalistic tendencies to use certain chemotherapy pairs with cisplatin, or even carboplatinum, but no pair of drugs emerges as superior, and three drugs seems to increase toxicity without adding a survival gain. The international standard of care for stage IIIa patients remains chemoradiotherapy, but the drugs, the timing of the two modalities (concurrent or sequential) and the penetrating question of whether a select subset might benefit from more remains unanswered. Underpowered phase III and highly publicized phase II studies have tried to establish chemotherapy for two or three cycles followed by surgery. Even for N-0 patients and for N-2 patients, the complete response is in the single digits, or if reported higher, the confidence interval includes less than 10% (Pisters et al). Many have clamored for the newer chemotherapy agents introduced in the 1990's, particularly carboplatinum paclitaxel in the US, and while these are used, none of these have actually added substantially to the cisplatin plus a "V" drug combination.

Tri-modal therapy began with the SWOG trial 8805 (Albain et al). This trial's 120 plus patients provided the data that formed the basis and the hypothesis for the US Intergroup 0139 trial. The backbone of both trials is cisplatin etoposide and concurrent radiotherapy, 45 Gy preoperatively, or 61 Gy definitively in the non-surgical arm of the Intergroup trial. Those that had induction chemoradiotherapy had a 10 - 30% chance of complete pathologic response in N-2 nodes, and these patients had long term prospect of survival, whereas those with residual disease in nodes almost universally failed. Moreover, supplementary post operative therapy (post operative boost radiotherapy or adjuvant chemotherapy) only increased morbidity and did nothing to salvage these less than complete nodal responders.

The major trials addressing the addition of surgery remain inconclusive. The largest and purest is the US Intergroup 0139, where patients were randomized to chemoradiotherapy to full radiotherapy dose of 61 Gy or truncating the dose to 45 Gy when used pre-operatively, both concurrent with cisplatin etoposide chemotherapy (Albain 2). Despite a significant benefit in disease free survival, there was no significant benefit in overall survival. Subset analyses show a hazard to pneumonectomy, particularly right sided, and a potential for benefit in patients requiring lobectomies. The negative impact of right pneumonectomies on overall survival has been pinned on the tri-modal therapy implicating the radiotherapy. Martin et al first called attention to the identical 25% mortality from a Memorial series that used chemotherapy alone, and indeed many sources note increased mortality with the pneumonectomy by itself without any adjuvant therapy. Andre forecast from over 700 French patients with N-2 NSCLC that four factors were key: single station, single lymph nodes, clinically obvious nodes by imaging did worse than incidental nodes, and using neoadjuvant chemotherapy. VanMeerbeck and the EORTC recently reported a trial using 2 to three induction cycles of chemotherapy based on a platinum plus one other modern drug. Nearly half of the 579 patients registered were randomized to resection or radiotherapy, but 47% of patients did not proceed after induction therapy for a variety of reasons. Despite eliminating some of the most unfavorable cases during the induction treatment, there was no difference in median or five year survival. The US Intergroup has not been closed a minimum of 6 years, but at last report, surgery achieved 27% and chemoradiotherapy 20% 5 year survival (NS). The EORTC trial reported 16% versus 17% 5 year survival (NS) for patients randomized to surgery and radiotherapy respectively. Undoubtedly there were differences in selection and other factors between these studies, but the EORTC study had the more modern chemotherapy, and the US Intergroup study was less successful in administering the post